TROPICAL DISEASES

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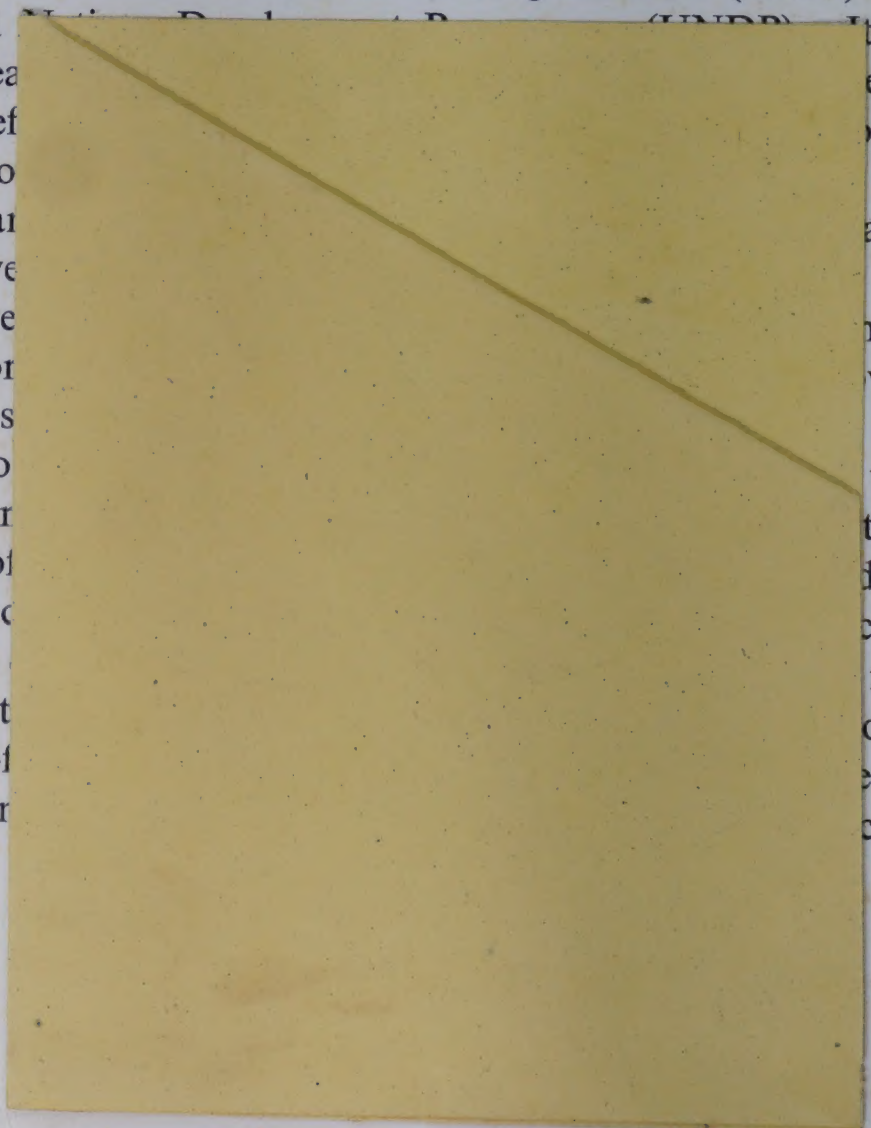
TROPICAL DISEASES

Many millions of the people living in tropical regions of the world are cut off from the main stream of social and economic progress. Victims of a heavy burden of disease as well as of harsh economic circumstances, they are not free to choose and plan a better future.

There is a growing awareness of these special problems of the tropical countries, and one main channel of response is through the work of the World Health Organization (WHO) and the United



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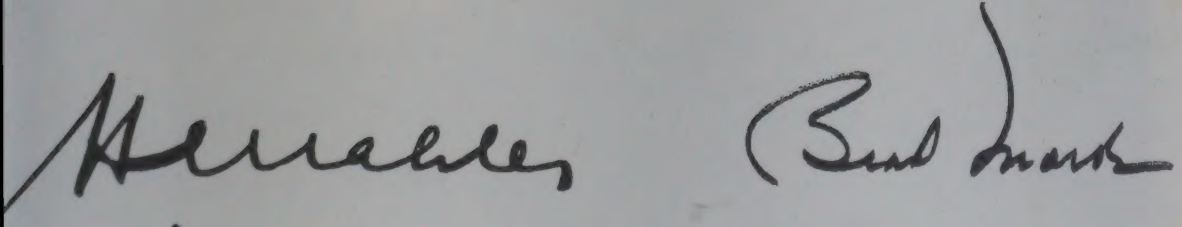
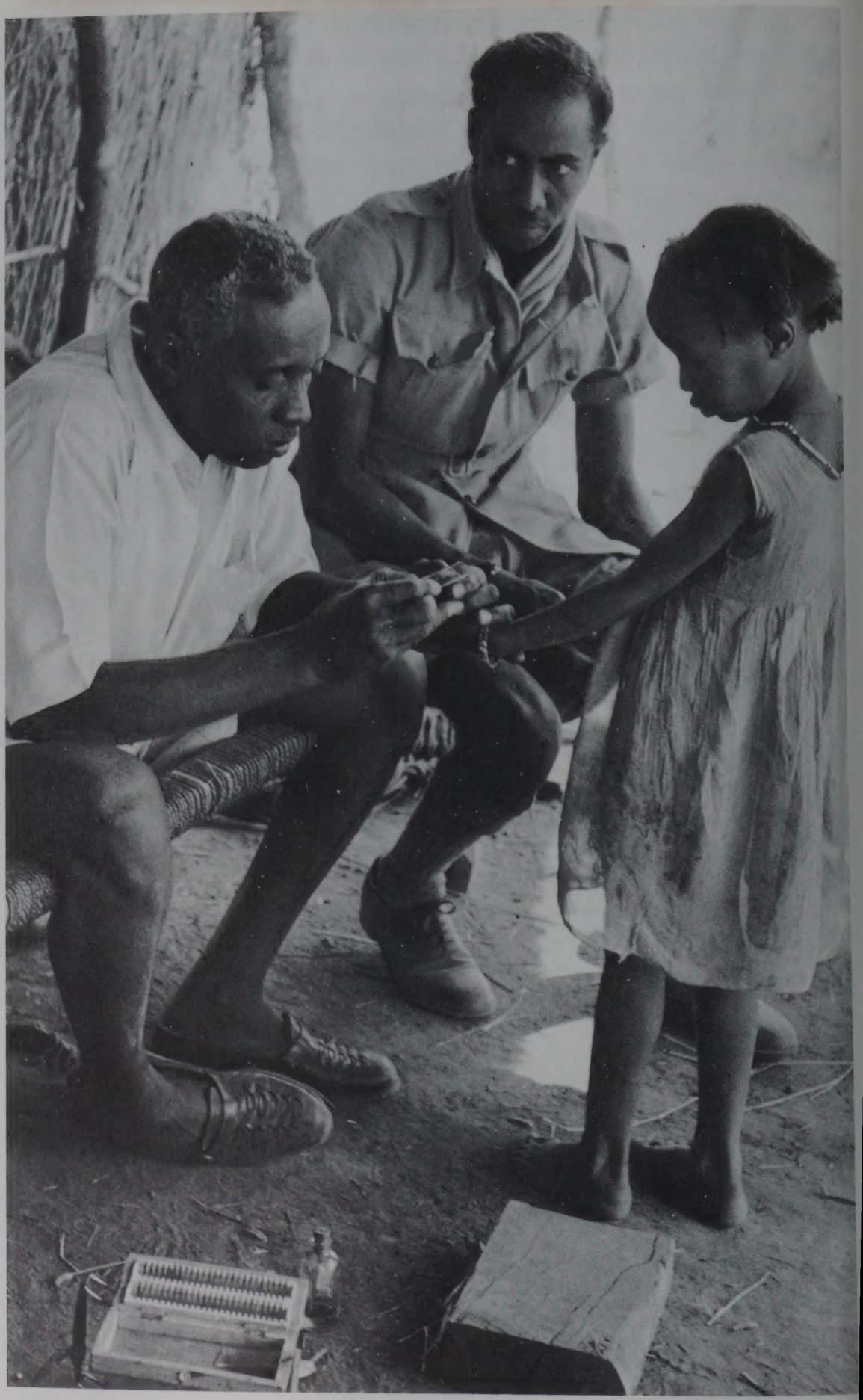
lrugs for malaria control are unable to stop transmission of the lisease throughout very large areas of Africa. Present remedies or other major tropical diseases—schistosomiasis, filariasis, rypanosomiasis, leprosy and leishmaniasis—are not practicable or large-scale use in many tropical countries. New tools are herefore needed.

WHO and UNDP recently launched a new Special Programme or Research and Training in Tropical Diseases to obtain these iew tools. Fundamental to this Programme is the involvement of the world's leading scientists and research institutions. But of qual importance is the fullest possible involvement of the tropical ountries themselves so that they may become competent, through raining and research, to deal with their own disease problems. We commend this booklet to your reading as an account of the challenges and opportunities. We hope to enlist your support for plan of action which holds a genuine promise for human betterment.

Dr H. Mahler
Director-General WHO

Mr B. Morse
Administrator UNDP





A medical worker takes a blood sample from a child in Sudan, where mosquito resistance to DDT resulted in a recrudescence of malaria and threatened to ruin one of the most promising development programmes in Africa.

THE BURDEN

Several hundred million people are affected by tropical diseases, and many more are at risk. Most of these diseases are chronic and long-drawn-out infections. Sometimes they lead to early death, but this only partly reflects the human suffering they cause.

Tropical diseases affect every aspect of human life from childhood onwards, and even when they don't kill they are debilitating: they can disable an entire population, prevent the planting or the reaping of crops, cause the abandonment of fertile and potentially productive land, and increase the effort required for survival.

At a time when most countries of the world plan and undertake activities to bring about social and economic improvements, tropical diseases stand as a major obstacle because people who cannot achieve minimal good health cannot promote or fully benefit from development.

The Gezira case history

Many examples can be found of the impact of tropical diseases in destroying the hopes for a better life by undermining the efforts to achieve it. That of the Gezira project in Sudan is typical.

Early this century, the possibilities for economic development and social progress were remarkably well demonstrated in this triangle-shaped area lying between the White Nile and the Blue Nile south of Khartoum. The Gezira was a sparsely populated, semi-arid savanna when the completion of the Sennar Dam on the Blue Nile made possible the reclamation of nearly half a million hectares of land.

Spectacular transformations gradually took place as living conditions of farmers improved and new immigrants were attracted by the magnet of a self-sufficient, decent life. Within a few decades, the Gezira became the most densely populated and the most prosperous agricultural region of Sudan.

It acquired a unique character. The typical Sudanese thatched round huts became interspersed with the rectangular whitewashed mud or brick houses built by the immigrants from Chad and Nigeria or provided by the government, and with the camel-hair tents of the nomads who came during the cotton-picking season. Schools, dispensaries, health centres, and hospitals jostled with white minarets and the traditional markets—social centres for a busy, white-clad, white-turbaned or white-veiled population.

At first, reclaimed land was almost exclusively planted with cotton, the country's cash crop, known the world over for its superior quality. This crop permitted a simple and effective mosquito control measure: peripheral irrigation ditches were

left to dry out every few days, never remaining full for a whole week—the time required for the complete development of mosquitos from egg to adult. This, together with the use of larvicides and the speedy treatment of the relatively few malaria cases, kept the disease under control.

Gradually, secondary crops were added: millet, wheat, groundnuts and, later on, rice. This meant that the periodical drying out of the canals had to be abandoned, with the result that larvae of *Anopheles gambiae*, the principal malaria-transmitting mosquito in the region, could reach maturity.

Malaria strikes

In 1950, after a season of particularly heavy rains, malaria struck. It spread rapidly from village to village, affecting thousands of people within weeks. More than half of the total labour force of the Gezira was infected by *Plasmodium falciparum*, the predominant parasite species in the region and responsible for the severest form of malaria. Hundreds of people died, and so many were weakened that fully one-third of the crops went unharvested. To the incalculable human cost was added the economic loss of about 10 million dollars.

This marked the beginning of a long, costly fight against malaria and its vectors—mosquitos. These insects gradually developed resistance against major insecticides: first to dieldrin, then to DDT. A World Health Organization survey in 1970 revealed "an extraordinary high tolerance of mosquitos to DDT". The use of DDT was abandoned in the Gezira. Larviciding became irregular and by 1974 it was entirely discontinued owing to a shortage of larviciding oil. Meanwhile, malaria progressed.

In 1961, a survey of 16 villages had shown that malaria was endemic in 7 of them. By 1975, it was endemic in all of the 16. In some villages, more than half of the people were infected with malaria.

A major effort is now under way and an attempt is being made to use massively all available weapons against malaria. Armies of "mosquito men" have been trained to spray malathion, a new insecticide to which mosquitos are still susceptible. Households are regularly surveyed and drugs are used on a large scale in the hope of reducing transmission. Larviciding operations have been resumed, and experiments are under way to test the possibility of seeding canals with fish that feed on mosquito larvae.

Nevertheless, a parasite transmitted by a mosquito has endangered one of the most promising and dynamic developments in Africa. Who can tell what the Gezira would be like today had not a tiny micro-organism, invisible to the naked eye, interfered with man's will to better his lot?

Disease as a way of life

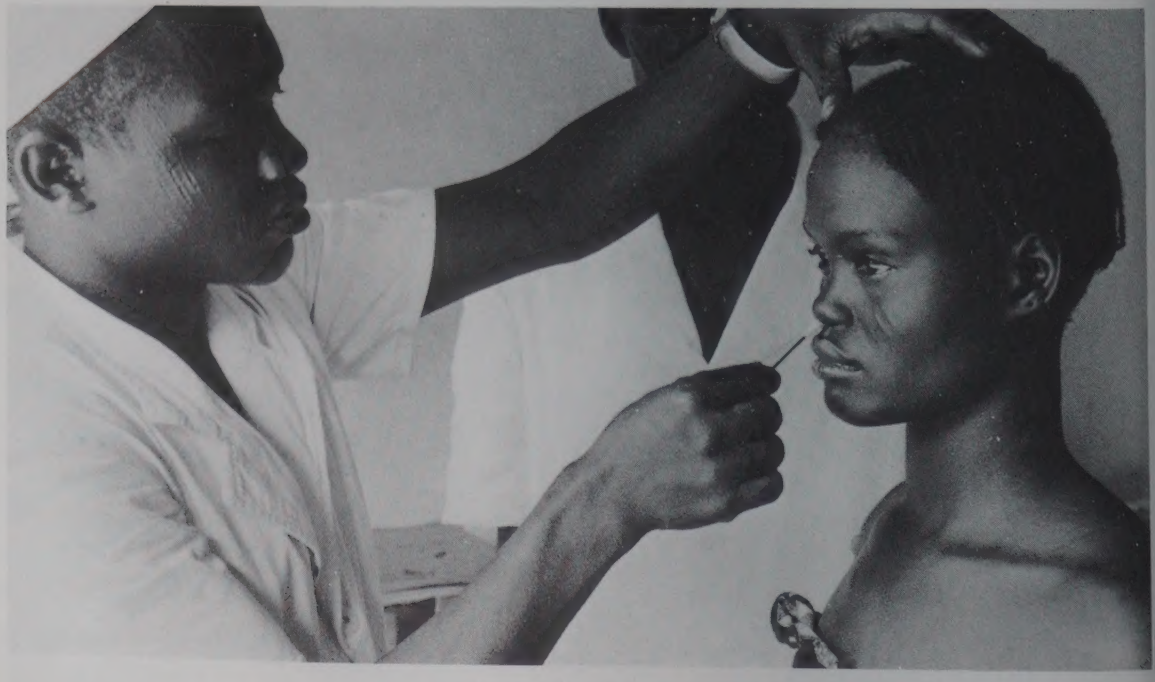
But this is only a small part of the picture. Dr David Rowe of the WHO Special Programme for Research and Training in Tropical Diseases writes:

"It is difficult for those living in temperate climates with good standards of public health and medical care to realize the impact of disease on rural communities in the tropics. For example, if you happen to be born and grow up in rural Africa you are liable to harbour four or more different disease-producing organisms simultaneously. And yet, as a parent, you must be fit enough to work, or your

The waters of the Nile bring fertility to Egypt and Sudan, but they also harbour a water snail that transmits the small worms that cause schistosomiasis.

A medical assistant in the Gezira examines a malaria patient.

In Mexico : the face of malaria.



In Africa : examination of nasal mucus for the presence of the leprosy bacillus.

family will starve. In your village every child at times suffers the paroxysms of malaria fever and you and your wife will mourn the death of one or two children from this disease. The snails in the village pond carry schistosomiasis, and you do not consider it unusual when your children pass blood in their urine."

"You take for granted the disfigured faces and fingerless hands of the beggars in the village street suffering from leprosy. If you live near a river where blackflies breed, one in ten of your friends and neighbours will be blind in the prime of life. You know that waves of killing diseases such as measles and meningitis and perhaps sleeping sickness are liable to strike your village. But, lacking effective remedies, you tend to philosophize in the face of sickness. You make the effort to walk the ten miles to the nearest dispensary when you or your child is ill, but there may be no remedies, and it may be too late..."

The enemies within

Malaria is one of the most widespread diseases in the world, affecting some 200 million people. In some regions, malaria transmission is so intense that present efforts at mosquito control and disease treatment are totally inadequate.

In Africa, about one-fourth of all adults suffer from malarial fever at one time or another, and others are infected though they have developed a relative immunity and rarely have attacks. After the age of 12 months, almost every child in tropical Africa has malaria; at least one million children die of the disease every year. In other countries, such as India and Sri Lanka, where malaria had regressed before, it is now resurgent.

Schistosomiasis (Bilharziasis)

Schistosomiasis is an insidious and debilitating disease caused by small worms belonging to the group of parasites called trematodes or flukes. The adult schistosome worms live in the blood vessels of infected persons. The most widespread species is *Schistosoma mansoni*, which affects the bowel and is prevalent throughout Africa, the Middle East, and eastern parts of South America. Three other species also commonly infect man, two of which affect the intestine while one damages the bladder and, later, parts of the urinary system.

The eggs of the parasite are passed out in the faeces or urine of infected people and develop into larvae in fresh water. Here, they infect freshwater snails, in which they multiply, and then release large numbers of free-swimming larvae (known as cercariae) which can penetrate through the skin of a person entering the water.

Once in man, the larvae find their way into the small blood vessels of the large intestine or bladder, where they mature into adult worms of both sexes (the female lives in a fold along the body of the male).

The females are egg-laying machines. For possibly five years eggs are laid continuously and this process may last as long as 20 years in a small proportion of patients. Eggs that are not excreted lodge in either the bladder and adjacent organs of the genito-urinary system, when *S. haematobium* is the infecting parasite, or in the intestine and liver, when *S. mansoni* or *S. japonicum* is the invader.

In the advanced stages of urinary schistosomiasis the constant passage of blood in the urine is characteristic and the small contracted bladder induces difficulty

and marked frequency in urination. In some tropical areas, schistosomiasis of the bladder is associated with cancer.

During the later stages of the intestinal types of schistosomiasis, lack of appetite, nausea and loss of weight are frequent together with intermittent bouts of diarrhoea and passage of blood in the stools. The liver and spleen enlarge, fluid collects within the abdomen producing a bloated belly while, in contrast, the remainder of the body shows emaciation.

Individual cases can be cured, but the injection of anti-schistosomal drugs, some of which contain antimony, can cause serious side-effects.

Schistosomiasis is often a disease of rural development, as artificial lakes and irrigation canals are sources of infection containing very large numbers of larvae. This problem has been encountered in Egypt and Sudan since the building of the High Dam at Aswan, and in Ghana as a result of the construction of the Akosombo Dam on Lake Volta. Similar problems have afflicted northern Nigeria where the proportion of the population infected around the lake created by the Kainji Dam has doubled in three years. Incidence has also increased in the Gezira region of Sudan. Even in the semi-arid Arabian peninsula, irrigation projects have resulted in the spread of the disease to regions where it did not previously exist.

The glass specimen trays hold parasite-carrying snails being studied at a laboratory in Leyte, Philippines.

Filariasis

Filariasis is another widespread disease which in various forms affects about 300 million people throughout the world. There are at least eight filarial parasites that infect man. *Wuchereria bancrofti* and *Brugia malayi*, transmitted by mosquitos, infect some 250 million people, mainly in West, Central and East Africa, Egypt, the Malagasy Republic, the Indian subcontinent, South-East Asia, China, the Pacific islands and the Philippines.

The adult worms live in the lymphatic vessels and lymph nodes, obstructing the flow of lymph, causing inflammation and swelling (elephantiasis) of the arms, legs, and genitals.

Another filarial parasite is *Loa loa*, which is transmitted by a type of horse fly. It is prevalent in Cameroon, the Congo, southern Nigeria, and Zaire. Adult worms move around the subcutaneous connective tissues, producing the characteristic Calabar swellings, and sometimes cross the white of the eye, causing great discomfort.

River blindness

The most dramatic form of filariasis is onchocerciasis or river blindness caused by the worm *Onchocerca volvulus*, which is transmitted by a small insect, barely 3 mm long, with the ominous scientific name of *Simulium damnosum*—the blackfly.

Like many insects in the tropics, the female blackfly feeds on blood, and its bite can transmit the larvae of *Onchocerca volvulus* to the person on whom it feeds. Once in the human host, the larvae develop into long, threadlike worms less than a millimetre across but up to half a metre long. These worms live up to 15 years and produce millions of embryos that invade the skin and eyes.

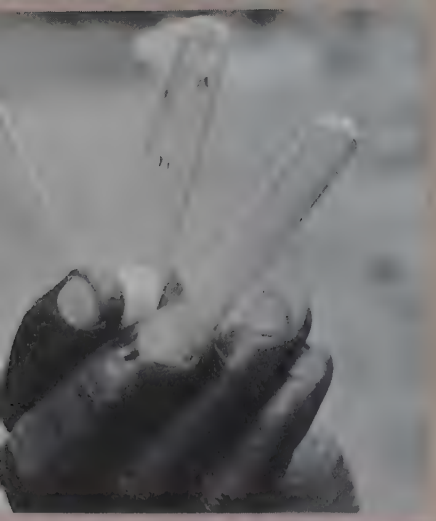
The blackfly breeds only in fast-flowing water rich in oxygen and nutrient matter, and the worm develops inside the fly only at a temperature of 18° C or above. In other words, the disease can be transmitted in circumstances existing chiefly in tropical regions where it is hot and where there are fast-flowing rivers.

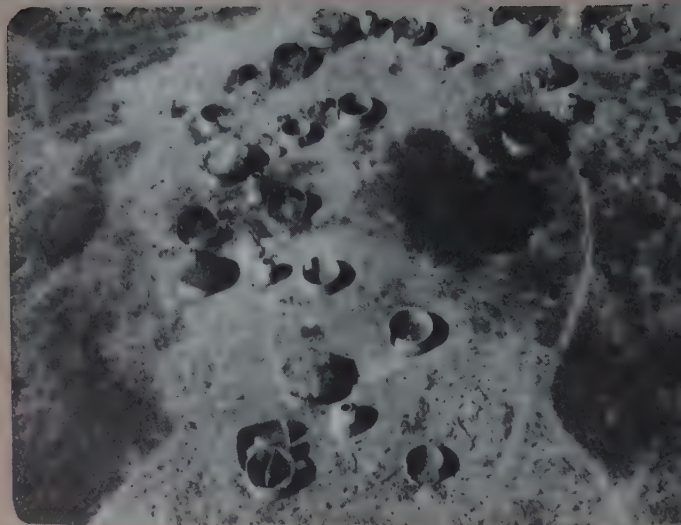
Because of the heat, farmers in such areas work naked from the waist up and with legs bare. Thus they are exposed to the merciless attacks of blackflies. In endemic regions, the blackflies are so numerous that there is no way of keeping them off. A man may suffer several thousand blackfly bites a day, each of them a source of irritation and a potential source of infection.

At first the infection usually goes unnoticed. The larvae develop very slowly. A year or more later they become adult worms that settle in tissues under the skin and produce characteristic nodules. Each female worm produces thousands of embryos which invade the skin and may cause uncontrollable itching. Sometimes they also invade the eyes. The victim may then go slowly blind.

In some regions of tropical Africa the sight of a young child leading a string of grown men through a village is a common one. The men look old, although few of them are over 35 or 40. Some are like walking skeletons, their bones protruding under the skin, their eyes sightless. The child leading this macabre procession is, most likely, also infected.

Many adolescents already show the effects of the disease: the skin is wrinkled and nodules containing adult worms can be seen under the surface. Some youngsters, already suffering from partial blindness, one of the early manifestations of oncho-





cerciasis, walk hesitantly round the village at dusk, their hands extended in front of them, feeling for obstacles they cannot see.

In the upper basin of the Volta River the number of onchocerciasis sufferers is estimated at over a million, and many thousands are blind. A special onchocerciasis control programme has been launched in Benin, Ghana, the Ivory Coast, Mali, Niger, Togo and Upper Volta, seven of the most severely affected countries. The programme includes the insecticide spraying of inaccessible rivers from helicopters to control the blackfly and halt transmission of the disease. The treatment of persons already infected is made difficult by the lack of non-toxic drugs that are effective against the adult worms.

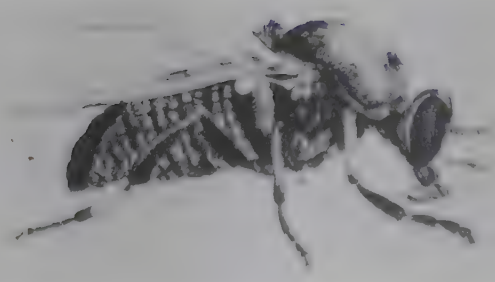
Other tropical diseases

Malaria, schistosomiasis and filariasis are the three massive tropical infections. But there is a score of other tropical diseases, most of them caused by organisms that prey on man—his liver, blood, heart, brain, and gut.

There are roundworms and flatworms that invade the intestine; hookworms that feed on the membrane of the small bowel; single-cell amoebae that attack the intestine and liver; corkscrew-shaped trypanosomes that burrow into the brain to cause sleeping sickness or, in South America, Chagas' disease (a form of trypanosomiasis that damages the heart); the slowly reproducing leprosy bacilli that mutilate and disfigure; intracellular parasites that cause leishmaniasis, with its two particularly severe forms: *espundia* in South America, which eats away the face, and visceral leishmaniasis or kala azar, fatal within two years if not treated.

Such is the added health burden carried by those peoples who live in tropical countries.

Control of onchocerciasis, or river blindness, at present depends on destroying the vector, Simulium damnosum*—the blackfly. The sequence shows, from left to right and top to bottom : blackfly larvae, enlarged to seven times life size ; a dam with fast-flowing water, where the blackfly larvae develop ; captured blackflies ; a blackfly, slightly over 2 millimetres long, starts feeding on human blood ; the same fly, bloated after feeding ; adults blinded by onchocerciasis are led by children ; a "blind village", which has been abandoned.*



Female Simulium damnosum, *vector of onchocerciasis.*

Trying out a new insecticide against malaria. In this photo, a member of the field research team is shown checking a mosquito breeding-place.

MOSQUITOS

There are very many different species of mosquitos, and all share certain common characteristics. They lay their eggs in water, and the larvae that come out of these eggs live in the water, breathing air through a kind of tube, somewhat like the snorkel of a submarine. In a week or more larvae become pupae, a transitional, immature form, and then adult mosquitos.

There are mosquitos all over the world, not only in warm tropical countries, where they are present all year round, but even in cold, northern regions such as Alaska, Greenland or northern Siberia.

The feeding habits of male mosquitos are much like those of the butterfly, limited to extracting nutrient substances from vegetation. But the females of certain species need human blood. These females have a proboscis, a tubular sucking organ capable of perforating the skin of man and animals. Their highly perfected bloodsucking system makes use of anaesthetic substances in the saliva, injected immediately at skin penetration, which may render the bite totally painless.

The saliva thus introduced into the host can also contain disease-causing organisms: parasites that cause malaria and filariasis, and viruses that can cause yellow fever, dengue, and encephalitis.

Four species of mosquito-borne malaria parasites can infect man: *Plasmodium falciparum, P. vivax, P. malariae,* and *P. ovale*. They provoke different forms of disease and react differently to antimalarial drugs.

Inadequate weapons

There are ways of treating individual cases of malaria, and ways of preventing them. But no single method has been developed that succeeds in protecting all of the people at risk or treating all those affected by the disease.

One possible approach is to attack the mosquito itself, the "vector". DDT and other insecticides have permitted spectacular successes in some parts of the world. In India there were 75 million cases of malaria in 1935, and a vigorous vector control campaign reduced the number to 60000 in 1962.

But several factors come into play to prevent the total eradication of malaria in many areas, and even to reverse the trend in others. Mosquitos have developed resistance to some insecticides and in the past few years the cost of insecticides has more than doubled. The cost of operating vehicles has also increased and, in addition, international assistance programmes have been reduced.

As a result, many countries simply can no longer afford to carry out antimalarial campaigns as vigorously as they have done in the past. Thus in India, for instance, the number of cases rose from a low of 60000 in 1962 to more than four million in 1974 – a 70-fold increase. In Africa, the situation is even more serious since

there is no hope for large-scale antimalarial operations in the foreseeable future. Dr Adetokunbo O. Lucas, former chairman of the Nigerian Medical Research Council, who has been appointed director of the WHO Special Programme for Research and Training in Tropical Diseases, points out that several intensive, well-supervised pilot and research projects in the African savanna have shown that infection is so deeply entrenched in the environment that spraying of insecticides and drug distribution are not sufficient to interrupt transmission.

Antimalarial drugs

For centuries, malaria has been treated with the bark of quinquina (or cinchona), a tropical tree, from which quinine was isolated in 1820. Quinine is the oldest and one of the most efficient antimalarial drugs, attacking the parasite when it develops in the red blood cell. But it can become dangerous when used in high doses, and even in low doses for people who are sensitive to it. Vomiting, diarrhoea, headaches, troubles of vision and hearing, even deafness, are among the side-effects.

Other antimalarials have since been developed, notably chloroquine, synthesized in Germany in 1934, and its derivatives. These 4-aminoquinolines are among the major antimalarials used today. There are, however, limitations concerning their utilization on a large scale in endemic regions. Some require prolonged administration when a person has been infected, others must be given regularly whenever one risks exposure to infected mosquitos. Shortage of health care facilities in most endemic areas makes this impossible, and in most of the affected countries a sufficient increase of health personnel is not foreseeable in the near future.

Furthermore, in vast regions of the world the parasites have become resistant to some of the major drugs. This is a very dangerous situation. For instance, *Plasmodium falciparum* resistance to 4-aminoquinolines occurs in some countries in South America, Asia, and the western Pacific. In Asia resistant strains have progressed westwards to reach the Indian subcontinent. If resistance crosses the Arabian peninsula, it could represent a great threat to the African continent, where *Plasmodium falciparum* is the main malaria parasite and chloroquine and other 4-aminoquinolines are the major antimalarial drugs.

Clearly, the existing antimalarial drugs are insufficient for the operational demands of a control programme, and there has not been great fundamental progress since the synthesis of chloroquine more than 40 years ago.

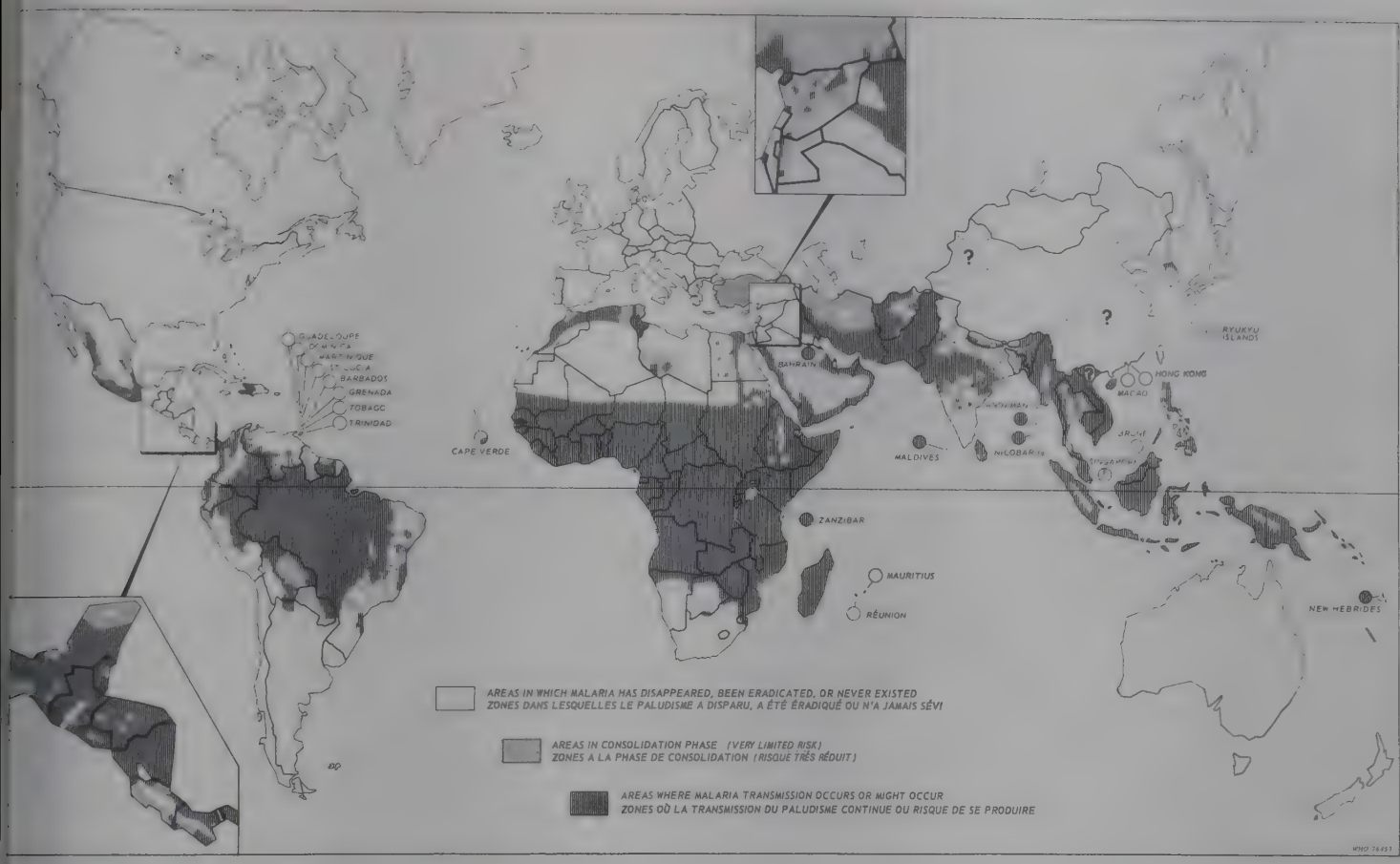
The promise of vaccines

There is promise in recent research for a malaria vaccine, but progress is slow although it is known that many infected people do develop an important degree of protective immunity.

The picture is similarly disappointing with regard to most other tropical diseases. There are no fully satisfactory drugs to control or eradicate them, and no vaccine to prevent them.

Yet, modern biomedical science has progressed in giant steps. In the past 20 years or so it has unveiled some of the deepest secrets of life and made it possible to alleviate previously incurable diseases.

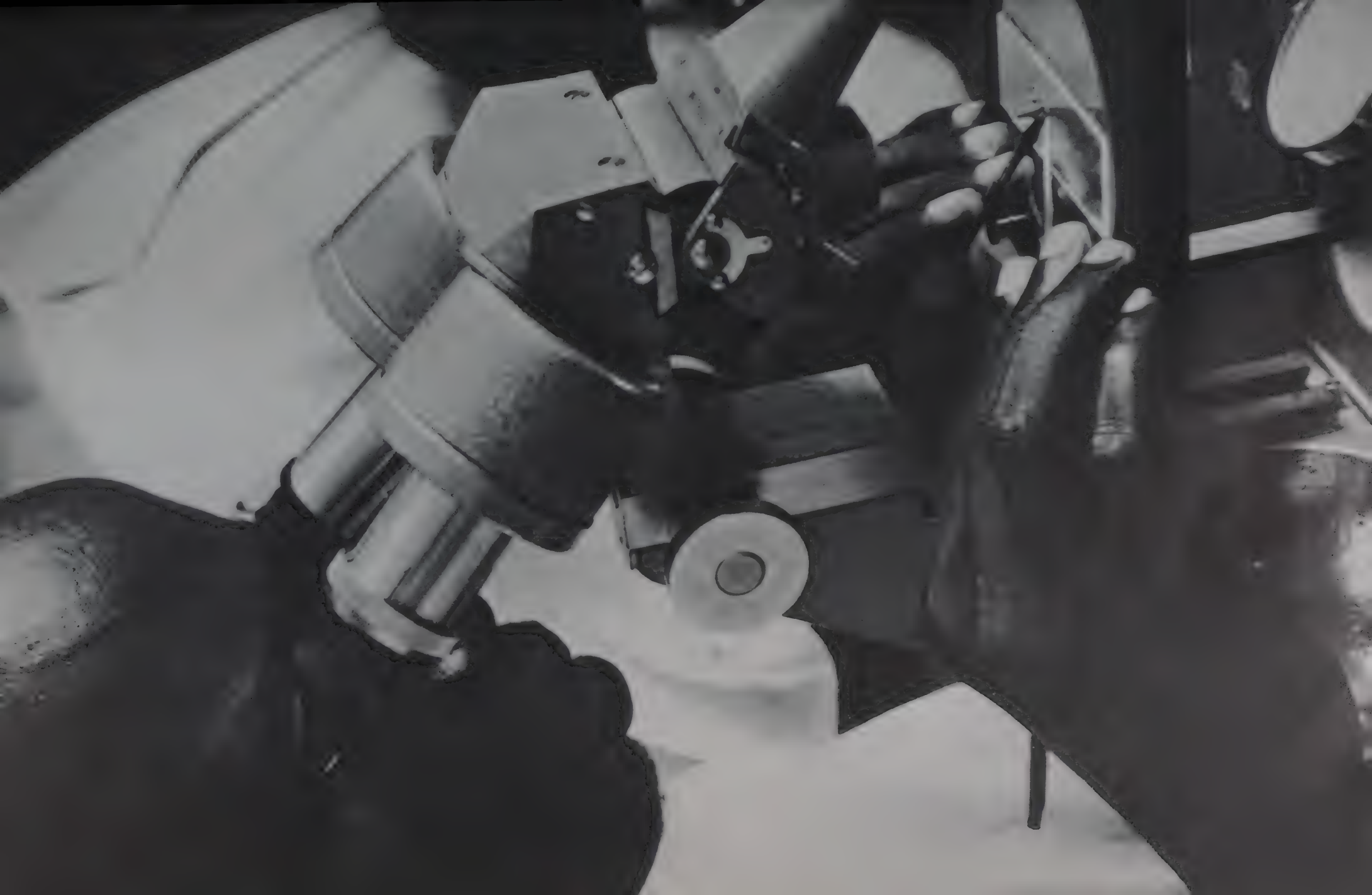
But it has not given tropical diseases the attention they deserve, even if they are judged only by the simple criterion of the number of people they affect.



Shading indicates areas at risk for malaria.

As published in the WHO Weekly Epidemiological Record, Vol.51 ; No. 24, Pages 190-191, 11 June 1976.

Adult Anopheles stephensi, *a mosquito that transmits the malaria parasite.*



A PLANNED COMMITMENT

Science today has a deep insight into the nature of life processes. Modern molecular biology has permitted the understanding of the genetic code, which is far more complex and infinitely smaller in scale than any man-made integrated electronic circuit. We can now decipher the code used to transmit the genetic message from generation to generation, and we know the path of transmission from the gene to the cell-factory that will produce whatever has been ordered. We know that the basic mechanism is the same whether the end product is a bacterium, a parasite, or a man.

In the 1970s, a gene was put together in the laboratory and the chemical and spatial structure of immunoglobulins, responsible for the organism's defence against foreign aggression, was analysed and described. Genetic engineering now makes it possible to break up genetic material and rearrange it in combinations unlikely to have occurred in nature. The possibility thus exists that common gut bacteria may be "instructed" to produce antibodies against harmful viruses or to synthesize protein from atmospheric nitrogen.

This extraordinary progress in molecular biology was accompanied by certain spectacular advances in medicine—the result of conscious, planned commitment of skilled manpower towards selected goals.

Vaccines to prevent, and drugs to treat, many of the diseases that have plagued humanity have been developed. Sophisticated treatments, using hormones and hormone-like substances, anti-viral chemicals and enzymes, have permitted the treatment of hitherto incurable diseases. Neuro-active drugs have made possible new approaches to the treatment of mental illness, and cancer research has made some forms of the disease curable.

The neglected diseases

But what of the tropical diseases that are, as they have always been, a major plague of humanity?

Here the natural lag between discovery and application has been prolonged and continuing. The broad base of knowledge available has not yet been exploited for a concerted attack against the tropical diseases. They have benefited, of course, from some of the "fallout" of research. But in relation to the number of people they affect and their impact, they have been grossly neglected. The late Professor Jacques Monod, a Nobel-Prize-winner in molecular biology, called this neglect "a disgrace".

A mere pittance of money and effort goes towards tropical disease research. Total worldwide annual expenditures devoted to research on all tropical diseases is about US $30 million, the cost of building a few miles of motorway.

Biomedical research has not yet been applied to tropical diseases in the methodical, purposeful fashion which has made it possible to answer some of the fundamental riddles of life and to develop the powerful tools of modern medicine.

"The comparatively modest progress in the development of new control technologies for tropical diseases is in no sense an indictment of the professional researchers in this field," points out Professor G.J.V. Nossal, Director of the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, and consultant to the WHO Special Programme, "rather, it is the result of disordered global priorities in health research which have limited the supply of such researchers... The Special Programme is conceived as a giant step toward rectifying this imbalance."

We simply do not know enough about the biology of the parasites or how they elude the defences of their human hosts. Our ignorance is a barrier to more intelligent implementation of control measures. A new approach must be made.

To study the enemy

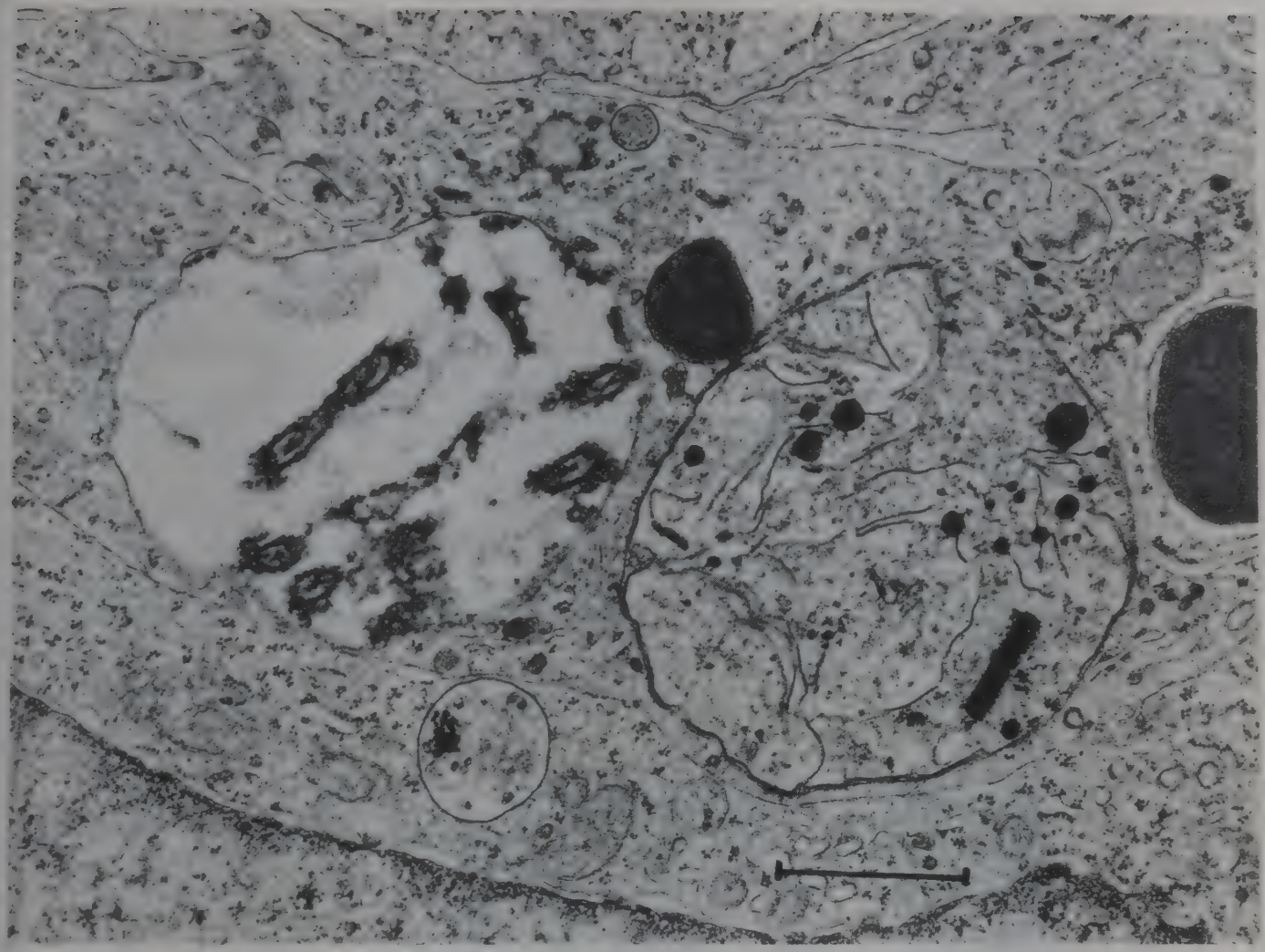
Parasites are small animals belonging to lowly groups: protozoa and worms of various kinds. In most cases they are completely incapable of independent life and rely for survival on the highly specialized environment provided by two or three, or sometimes more, successive hosts.

"When we come to think of it," says Professor Christian de Duve, another Nobel-Prize-winner in medicine, "they really have major weaknesses and must be quite vulnerable. My strategic recommendation, therefore, is that the forces of the new biology be enlisted for a detailed analysis, at the cellular, subcellular and molecular level, of the various parasites that infest man, and of their relationships with their human and animal hosts. I have no doubt that out of such a study, powerful new preventive and curative means will emerge."

Professor de Duve, who has unveiled the role of a specialized cell structure called the lysosome, has already carried out preliminary experiments that have confirmed the potential effectiveness of this approach.

"Lysosomes," he says, "are essentially miniature little stomachs, which occur in all cells. One of their principal functions is to serve in the digestion of food 'eaten' by the cells by a special capture process. As with humans, cells may be greedy or frugal, and they may exhibit a wide variety of tastes. Our purpose is to take advantage of these differences to kill certain cells selectively by poisoning their favourite food. To do this, we bind the poison to a carrier molecule in such a way that it will be released when it gets in the lysosome, that is, in the stomach of the cells that have eaten this poisoned food."

Experiments in mice carried out by Professor de Duve and his colleagues have indicated that such "selective poisoning" may be effective against *Trypanosoma cruzi*, the agent of Chagas' disease. This approach must also be tried against diseases such as schistosomiasis or onchocerciasis, caused by worms with very tough skins, whose weak points may be their "stomachs." Even the leprosy bacillus, which has no lysosomes of its own, may be vulnerable to lysosome therapy because it lives and proliferates within the lysosomes of some of the patient's cells.



Upper photo: *Parasites in lysosomes, as seen by the electron microscope. The large element on the right contains an apparently intact trypanosome, the parasite causing African trypanosomiasis. The element on the left contains an almost completely digested trypanosome. Bar in lower right-hand corner represents one-millionth of a millimetre.*

An electron microscope photo of a macrophage, one of the scavenger cells of the body normally responsible for killing infectious agents. However, some parasites such as Leishmania *find a way to take refuge, grow, and breed in macrophages.*

A major breakthrough

In April 1976, Professor William Trager of the Rockefeller University in New York, a member of the Special Programme's Scientific Working Group on Immunity to Malaria, announced that he had succeeded in maintaining for three months a laboratory culture of *Plasmodium falciparum*. The parasite had gone through many multiplication cycles in human blood cells.

This is the first time that a continuous *in vitro* culture of a human malaria parasite has been successfully established. It is a major breakthrough because large amounts of *P. falciparum* will now be available for research purposes, and there is renewed hope in the possibility of developing a malaria vaccine.

Immunization has permitted the control of many viral and bacterial infections. But there are no effective vaccines against the tropical diseases. There are, however, strong indications that vaccines could be developed against many of them if only the required concerted effort were undertaken.

Any disease agent is foreign to its host organism, and we should find out how it protects itself against rejection. Different protection mechanisms have already been identified in different organisms.

Recent research has shown, for instance, that the *Schistosoma* parasite has a very elaborate system to ensure its survival in spite of the immunological defences of the organism it invades.

When a free-swimming larva penetrates through the skin it is "recognized" as a foreign organism, and antibodies are produced against it. The attack, however, is still weak, and while it gathers strength the parasite has a few days to reach maturity. When it does, it covers its own antigens (the surface proteins that identify it as an enemy) with proteins that appear to be copies of the antigens of the host itself. It becomes a "wolf disguised in sheep's clothing".

One line of attack could be to immunize to increase the reaction against the larva, so destroying the adult parasite before it had time to protect itself.

Immunization against leprosy is likewise a feasible goal, and it is already actively pursued by a scientific working group of the Special Programme.

This microscope sequence shows the invasion of a red blood cell by a malaria parasite (arrow). The parasite becomes attached to the red blood cell (left) and there is a marked distortion of the cell (centre) followed by a relatively slow invasion of the red blood cell by the parasite.

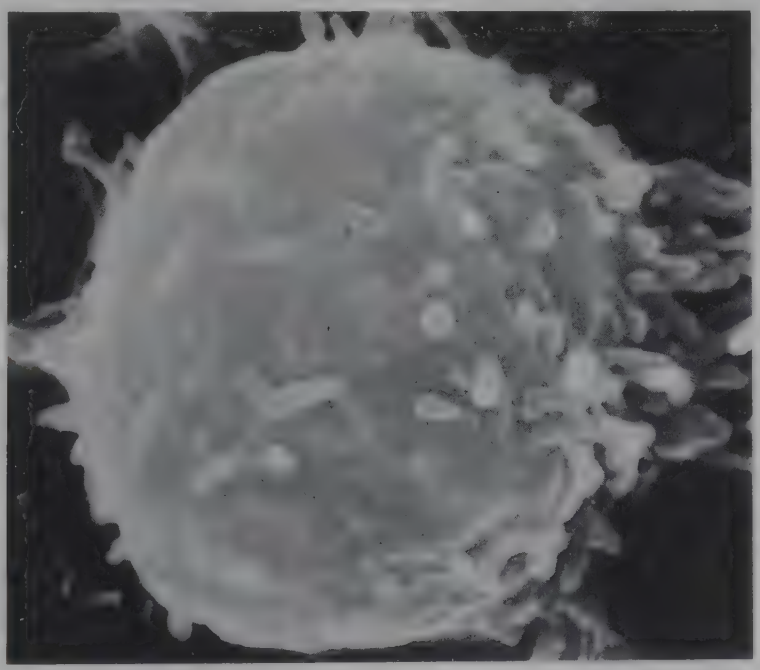
Towards high technology

But the development of vaccines, which could permit the control of parasitic diseases (and perhaps the eradication of some of them), may require the input of many disciplines, such as molecular biology, genetics and cellular immunology, in addition to parasitology. It may require, for instance, the availability of large sources of parasites free from contamination. This, in turn, may require the culture of insect tissues in which to grow parasites. (The development of the poliomyelitis vaccine was made possible because scientists learned to grow mammalian cells outside the body by the technique known as tissue culture.)

Insect tissue culture may, in turn, require the use of sophisticated biophysical fractionation methods to separate different classes of cells from one another. Also, we need to know more about the biology of the parasite and the mechanisms by which it eludes the defences of the human host. This knowledge may require deep insight into the molecular organization and peculiarities of the parasites.

In other words, frontier disciplines of biomedical sciences must be associated with parasitology in a concerted effort at developing vaccines. And this applies also to other possible approaches.

A lymphocyte cell (right), one of the white blood cells which are a major element of the organism's immunological defence system.



Preparation of measles vaccine at the Tirana, Albania, Institute of Hygiene and Epidemiology.

Drugs designed to interfere with enzymes are one of these. Enzymes are large molecules required in minute amounts by living organisms to carry out the most complex chemical reactions. Their action is very specific, but it has been shown that competitive molecules can be used to "fool" the organism and thus interrupt certain vital processes. For example, fertilized eggs of nematode worms, some of which are parasites of man, manufacture chitin, a substance which renders the cell tough and impermeable; since mammals do not produce chitin, interference with the enzymes needed to produce chitin could destroy the eggs without affecting the human host.

Both enzymology and genetics, as well as other scientific disciplines, can be involved in new approaches. For example, an important finding made in 1975 shows that some people possess a genetic factor that prevents the invasion of red blood cells by certain malaria parasites. This genetic trait conferring malaria resistance is called "Duffy negative" because red cells lack the Duffy antigen, named after the first person in whom it was discovered.

These Duffy antigens tell us which are the susceptible red blood cells. There is a "keyhole" on the blood cell, to which the parasite possesses the "key". If the keyhole does not exist (in Duffy-negative people) the blood cells are protected against the parasites. Laboratory experiments indicate that the "keyhole" can also be blocked by certain enzymes that remove the Duffy antigen.

Vector control

Vector control, likewise, can benefit immensely from research, especially in the area of biological vectors.

Experiments have shown, for instance, that tiny worms can kill the tsetse fly, the vector of the sleeping sickness parasite. Basic research into the biology of the insect and of its predator and exhaustive study of the potential ecological dangers of such an approach are obvious prerequisites.

These approaches are "high technology" approaches, such as have made possible the development of the poliomyelitis vaccine or of the vast range of antibiotics against bacterial infections. High technology remedies are the result of the application of fundamental knowledge. They are often spectacularly successful and, once available, they are usually cheap to produce and apply. But their development requires the commitment of skilled manpower and adequate budgets. One of the purposes of the Special Programme for Research and Training in Tropical Diseases is to evaluate possible approaches, plan specific lines of research, select the scientists most qualified to carry it out, and give them the means to work.

Rhodnius prolixus, *a vector of Chagas' disease.*

Phlebotomus papatasi, *a vector of leishmaniasis.*

A LEPROSY VACCINE?

How is goal-oriented research to be carried out under the Programme? An example is provided by the IMMLEP scientific working group, which met for the first time in November 1974. A scientific working group is a group of scientists working towards a defined goal, and IMMLEP stands for immunology of leprosy. The goal is to develop immunological knowledge of this disease with a view to perfecting diagnostic methods and eventually producing an effective vaccine.

Leprosy is one of the most perplexing infectious diseases. The leprosy bacillus was first described by Dr Armauer Hansen, a Norwegian, more than a century ago, but no claim of success with *in vitro* growth has yet been confirmed.

Hansen's bacillus (or *Mycobacterium leprae*), which in some respects resembles the bacterium that causes tuberculosis, is protected by a waxy layer and is characterized by its slow multiplication, which accounts for the long incubation period of leprosy—often several years.

At least 10 million people in the world are suffering from leprosy. The mode of transmission of the disease is not well understood. It is generally admitted that transmission is from man to man.

Some 15 years ago researchers succeeded in growing the bacillus by inoculating it into a mouse's footpad, but only small amounts of bacilli can be harvested with this technique. This shortage of bacilli was a major obstacle to further progress, including the possible development of a vaccine.

Armadillos make news

Then, a major breakthrough occurred. In 1971, researchers in Louisiana in the USA discovered that injection of *M. leprae* into nine-banded armadillos caused massive infection in some of the animals. For the first time, the harvesting of large numbers of bacilli for research became possible.

One of the important steps in developing a vaccine involves the methods for measuring, first in laboratory animals, then in man, the protective effect of candidate vaccine preparations.

These methods make use of antigens, the particular components of the parasite which, when introduced into an organism, trigger a specific immune response. The antigen preparation and purification is a complex task. One of the major objectives of the IMMLEP group has been to prepare antigens suitable for field use in skin testing.

By the time the IMMLEP group met again at the beginning of December 1975 considerable progress had been made on this first objective, the development of a leprosy-specific skin test, and three promising antigenic preparations had been

developed from infected armadillo tissue: one prepared in Venezuela, one in the United Kingdom, and one in the USA.

Some preliminary tests on human volunteers had been carried out. The results were promising, and the IMMLEP scientific working group decided to use the tests in areas where leprosy is not endemic (to avoid distortion of results by the possibility of previous infection) and where the influence of BCG vaccination, and of possible exposure to other common mycobacteria can be taken into consideration to the greatest extent possible.

Tests in England and Norway were due to start early in 1976, and a tight schedule of operations had to be set up. Some infected armadillos were available at the National Dermatology Institute in Caracas, and additional material was to be shipped there no later than 15 December 1975. Fractionation of antigens started immediately, and by early January 1976 the antigenic preparation was sent by air (on ice) from Caracas to London for coding and distribution to the various centres involved.

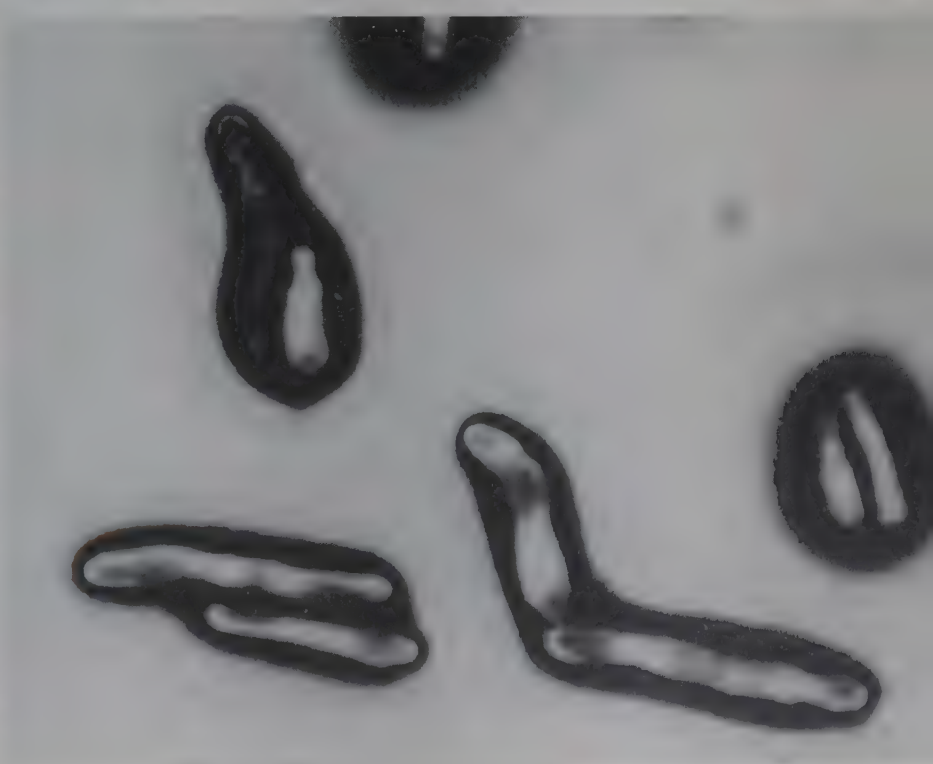
Methods based on the most up-to-date biomedical techniques were then used to analyse with precision the results of the IMMLEP trials. They include skin tests for delayed hypersensitivity, *in vitro* tests to determine immune response, and tests to measure the level of circulating antibodies combined with mycobacterial antigens.

These investigations must be performed by highly experienced personnel and often require sophisticated and costly equipment.

Thus another step was taken with development of a skin test, the diagnostic aid in the search for a vaccine against leprosy. There is no absolute certainty at this time what type of vaccine can be made or what type is needed for the control of leprosy, though the prospects for developing an effective one are hopeful.

The nine-banded armadillo, first source of large amounts of the leprosy bacillus.

Above: *Before a nurse administers the injection of dapsone for treatment of children with leprosy, the children are weighed and the amount of dapsone to be given is calculated by weight and marked on their backs.* Above right: *A mother, mutilated by leprosy, holds her child, already a victim of the same disease. They live in a lonely spot in the bush with a group of others who share their plight.*



Electron microscope view of the leprosy bacillus obtained from armadillo.

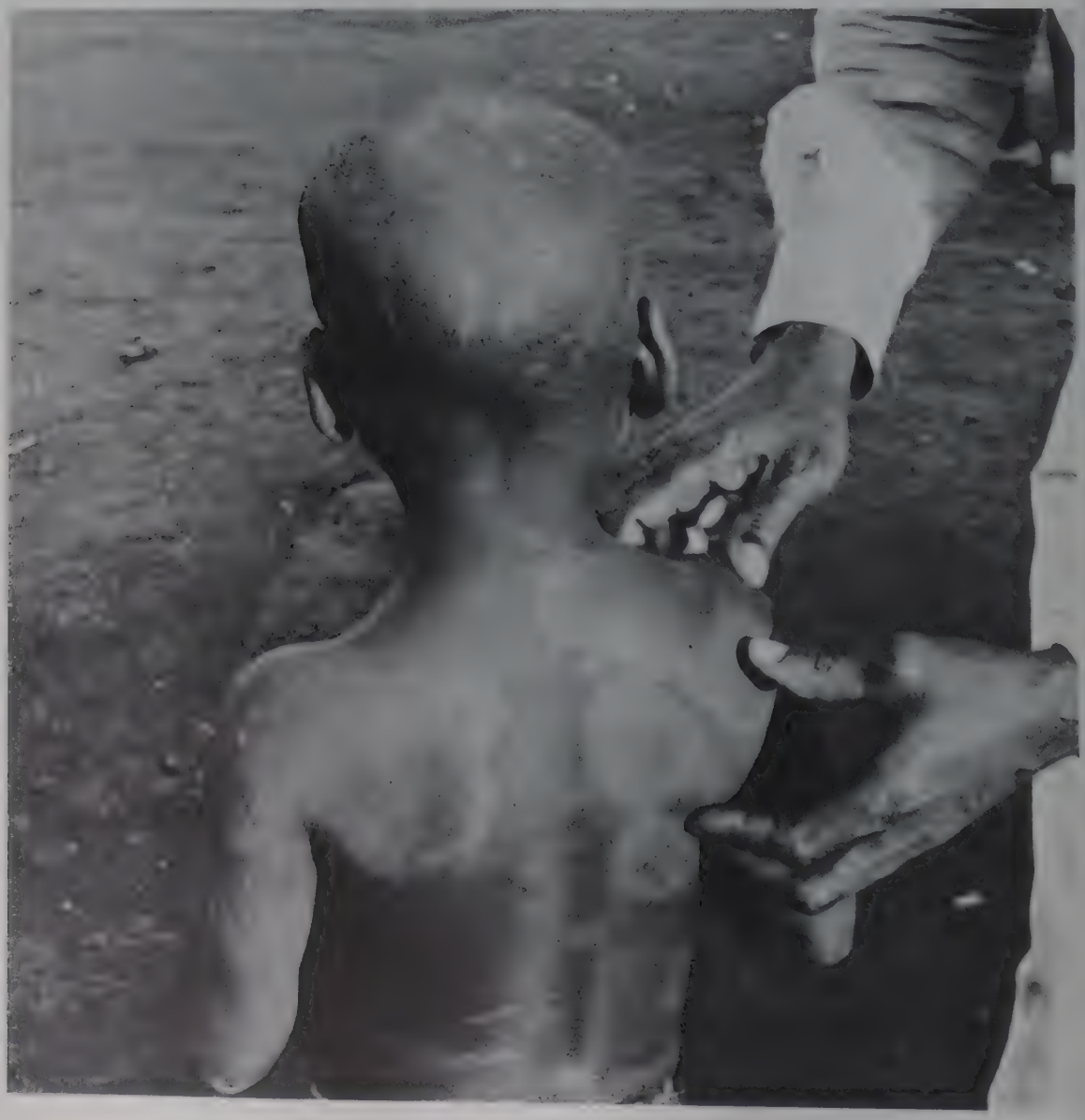
To break the deadlock

In one of its reports, the IMMLEP group indicated that, "Given a source of antigen, it is virtually certain that one or more of these agents can be adapted for use in a practical vaccine that would provide long-term protection against *M. leprae* and might even be used to break the immunological deadlock that develops in lepromatous leprosy."

Now, a tentative schedule has been established: if all goes well, field trials of a vaccine could start in 4 or 5 years, and would be followed by varying periods of observation which are required due to the long incubation periods of leprosy.

As the IMMLEP programme progresses with the improvement of diagnostic techniques (2 to 4 years), the possible development of a vaccine (10 to 20 years), and immunotherapy (4 to 6 years) it will be backed up and strengthened by better and more effective chemotherapy. For this purpose, a Chemotherapy of Leprosy (THELEP) programme is being formed.

These intensive research efforts can be expected to take us past a significant milestone in the century-old fight against leprosy.



This child, who lives in a leprosarium, shows early signs of leprosy.

AN ACTIVE PARTNERSHIP

Given adequate resources and a careful selection of priorities, new knowledge in biomedical sciences can radically alter the course of the uphill fight against tropical diseases, most of which are out of control.

Vaccines against leprosy and malaria can reasonably be expected in the next 10 to 20 years. Better knowledge of parasites will inevitably improve the prospect for vaccines against schistosomiasis, trypanosomiasis, and leishmaniasis.

Reliable and practical diagnostic techniques and better drugs, with less serious side-effects, will result from concerted research into parasite function and biology. Until now, most of the anti-parasitic drugs have been selected empirically through large-scale screening, rather than developed specifically to penetrate into the chinks in the parasites' armour.

The investment required is minimal compared with the results that can be expected.

In endemic areas productivity is frequently decreased, and during epidemics the entire work force of an area may be disabled, preventing the planting or harvesting of crops. The prevalence of diseases may dictate the distribution of a population. For example, human occupancy of large areas of Africa, Asia and the Amazon region of South America have been impossible due to malaria, trypanosomiasis, or onchocerciasis.

The impact of parasitic diseases on cattle and domestic animals should not be omitted from this balance sheet. In Africa alone, about 10 million square kilometres of land are infested with tsetse flies. If cleared of the vector, this land could provide for a potential cattle population of 125 million. Thus the Special Programme will work in cooperation with the International Laboratory for Research in Animal Diseases set up in Nairobi, Kenya, sharing with it fundamental knowledge needed to develop new tools for the control of trypanosomiasis.

The task to be accomplished is not an easy one. It is a major effort, and it represents more than a scientific endeavour. It is a form of operational research, requiring managerial skills, financial expertise, political experience, and organizational capabilities in addition to the specialized competence of scientific researchers.

Preliminary meetings concerning the Special Programme and scientific meetings devoted to specific diseases have already been held in Geneva and elsewhere. The Special Programme is co-sponsored by the World Health Organization and the United Nations Development Programme. During the first meeting in 1975, several countries and agencies contributed sufficient funds to carry on preparation and planning of the Programme for the first year in an attempt to determine the most efficient way to carry it out, to select participants, to determine goals, and to work out schedules and budgets.

A researcher in Iran examines snails for the presence of parasites causing schistosomiasis.

The plan

Discussions among experts in various fields of biomedical research, specialists in tropical diseases, health authorities of several countries, and WHO staff, indicated that a two-pronged approach was necessary:

- To enlist the specialized knowledge and technological facilities in different areas of biomedicine that are available chiefly in the industrialized countries.
- To associate this with research and clinical work already being carried out in the very countries most affected by major tropical diseases, by strengthening existing institutions, and training additional scientific personnel.

At the beginning, the Programme will focus on the institutions in one continent, the one that carries the major burden: Africa. The concept of the plan is global, however, and research centres on other continents will participate in it. It will concentrate on six diseases: malaria, schistosomiasis, filariasis, trypanosomiasis, leprosy and leishmaniasis, which constitute the crux of the problem.

The plan is to enlist and support existing laboratories and clinical research centres in several tropical countries and to develop new laboratories where necessary. It is hoped that many or all of the 25 or so medical schools in tropical Africa will become key participants in this work since the medical personnel being trained there will inherit the responsibility of providing health care in the region and of carrying out research on local disease problems. Already, the Government of Zambia has made a generous offer of facilities for a multidisciplinary tropical diseases research centre.

At the same time, research centres in industrialized countries and the pharmaceutical industry will share their knowledge in an active partnership with the Programme. Their aim will be to develop new remedies and promote scientific self-reliance so that people in different lands, facing different sets of conditions can solve their own problems with the best available means.

A child in Thailand is examined for enlarged spleen, a sign of malaria.

Below: *A health worker analyses samples of excrement and urine collected in a village.*

THE TIME IS NOW

As distances between all parts of the world are effectively shortened by modern systems of communication and transport, countries and people everywhere are growing increasingly interdependent. The words of John Donne written almost 400 years ago, "No man is an island, entire of itself", remain as a timely warning to us today. Without leaving our homes we are witness to events occurring in distant places, and we follow their progress with interest or concern. Even if we sometimes choose not to see or to hear, and for a time turn aside to attend to our own lives, we cannot escape involvement, and it is clear that a new global consciousness is emerging that was unprecedented in any earlier age.

One of the major challenges of our time is health. Good health is now widely recognized as a fundamental human right for all people, and acceptance of this proposition implies that human society must shoulder the burden and accord the highest priority to ways and means of achieving that goal.

How is this to be done?

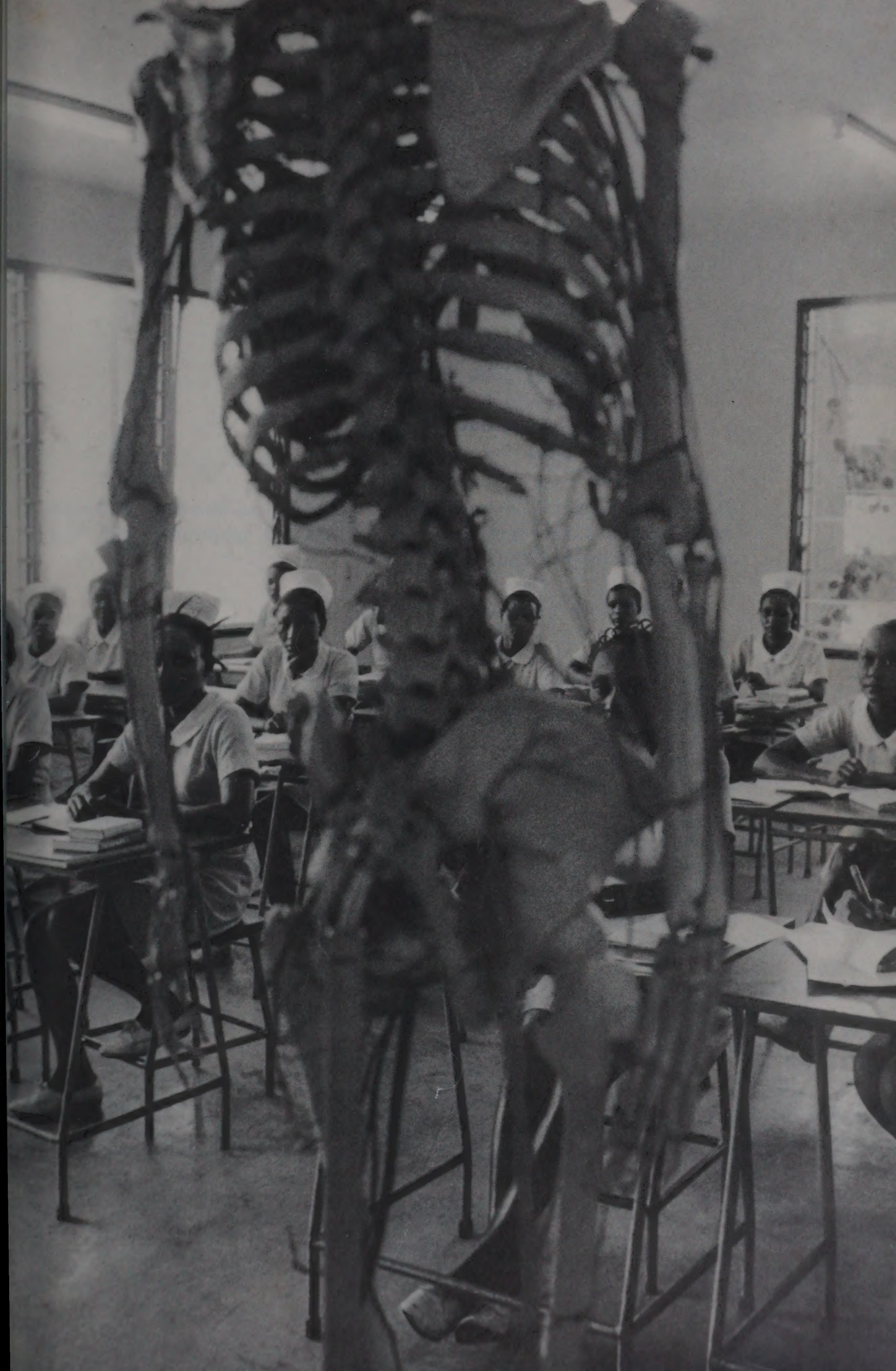
Science certainly has a paramount role to play. It has contributed to providing many with the means to lead a good life, but many more have been left out of the mainstream, struggling not only for a decent life, but for survival.

Goal-oriented science

If the goal of reaching an acceptable level of health for all within the next 20 or 30 years is to be achieved, the keystone will be political action. Sufficient priority must be given to health in relation to other goals such as industrialization and economic growth. An essential correlation is often ignored: in general, healthier people make more productive workers and wealthier citizens.

Health cannot be isolated from its social context. Poverty, malnutrition, poor hygiene, lack of education, inadequate housing, unemployment or poor working conditions, and pollution, as well as the presence of viruses, bacteria, parasites and other disease-causing organisms, are factors predisposing to ill health. The cumulative action of these factors leads at the present to unacceptable disparities. In some developing countries, as many as half of the children die before reaching their fifth birthday; childhood mortality rates in these countries are about 50 times higher than those in the developed world.

The conquest of major parasitic diseases may not mean health for all, nor can the purposeful harnessing of science guarantee their conquest. But it is certain that health for all cannot be achieved without this conquest and that this requires better tools, which science can provide. It would seem that the investment is minimal in comparison with the return that can reasonably be expected. The initial yearly cost of the Special Programme for Research and Training in Tropical Diseases will be US $15–20 million or about the cost of a single jet fighter aircraft



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